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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,906	03/19/2007	Yuki Naito	074439-0102	4892

22428 7590 10/31/2007
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EXAMINER	
PITRAK, JENNIFER S	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,906	NAITO ET AL.	
	Examiner	Art Unit	
	Jennifer Pitrak	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 9-12* is/are rejected.

7)☒ Claim(s) *6-8 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/29/06; 05/19/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Claim Objections

Claims 6-8 and 13 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Status

Claims 1-5 and 9-12 are under examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir, *et al.* (2001, Nature, v.411:494-498).

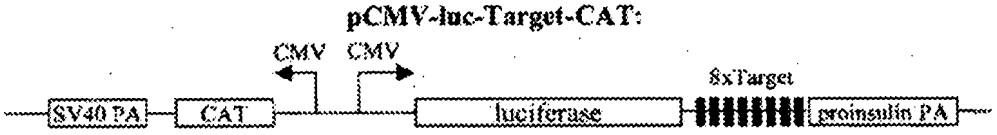
The claims are to methods for evaluating RNAi activity, comprising the steps of: supplying a target-expressing molecule, such as a vector that directs expression of a reporter gene, and a subject nucleic acid molecule, such as an siRNA, to be evaluated for its ability to direct target cleavage by RNAi into a cell-based or a cell-free expression system and detecting whether or not the target RNA has been cleaved.

Elbashir, *et al.* teach the use of siRNAs to induce RNAi of a luciferase reporter gene in Drosophila S2 or mammalian cells (first paragraph, p.495; Figures 1 and 2). The reporter plasmids and siRNAs were cotransfected into cells and luciferase activity was measured to assess target RNA cleavage. Thus, Elbashir, *et al.* clearly anticipate claims 1, 4, and 5.

Claims 1, 4, 5, and 9-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Zeng, *et al.* (2003, PNAS, v.100:9779-84).

The claims are to methods for evaluating RNAi activity, comprising the steps of: supplying a target-expressing molecule, such as a vector that directs expression of a reporter gene, and a subject nucleic acid molecule, such as an siRNA or a microRNA, to be evaluated for its ability to direct target cleavage by RNAi into a cell-free or cell-based expression system that is capable of RNA splicing. The claims are further drawn to a method of evaluating miRNA activity comprising a step of supplying into the expression system a control-supplying molecule which comprises a control sequence, which is not suppressed by the subject nucleic acid molecule and which encodes a detectable expression product, and wherein the control-supplying molecule is integrated into the target-expressing molecule.

Zeng, *et al.* teach the pCMV-luc-Target-CAT plasmid, which contains a cytomegalovirus (CMV) promoter driving expression of firefly luciferase and 8 repeated regions of a miRNA target sequence or a random target sequence as a control, and which contains a CAT reporter sequence that serves as a non-targeted control (Figure 1, p.9780), shown below.



Specifically, Zeng, *et al.* introduced this plasmid containing 8 copies of the miR-30 target region into human 293T cells along with plasmids directing the expression of either miR-30, which targets the miR-30 target region, or miR-21, which does not target the miR-30 target region, and with a control plasmid encoding β-gal (pages 9780-1 and Figure 2). After transfection of the 293T cells with these plasmids, the authors assayed for luciferase expression and mRNA levels (by northern blot) to determine whether cleavage of the reporter RNA had occurred (Figure 2). Thus, Zeng, *et al.* anticipate claims 1, 4, 5, and 9-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 9-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zeng, *et al.* as applied to claims 1, 4, 5, and 9-12 above, and further in view of Wang, *et al.* (1999, Anal. Biochem., v.269:198-201), Kramer, *et al.* (2001, CPMB, 15.1.7), and Ishaq, *et al.* (1994, PNAS, v.91:8283-7).

The claims are to methods for evaluating RNAi activity, comprising the steps of: supplying a target-expressing molecule, such as a vector that directs expression of a reporter gene, and a subject nucleic acid molecule, such as an siRNA or a microRNA, to be evaluated for its ability to direct target cleavage by RNAi into a cell-free or cell-based expression system that

is capable of RNA splicing. The claims are further to the method of RNAi evaluation wherein the target sequence is bordered by PCR primer-binding regions and wherein target RNA is quantified by RT-PCR, wherein the levels of target RNA in the presence or absence of the subject nucleic acid are compared and wherein one of the primer binding sites contains an intron within it, allowing for more accurate evaluation of RNA levels as amplification of the DNA template can be prevented (see instant specification at p.13, lines 14-24). The claims are further drawn to a method of evaluating miRNA activity comprising a step of supplying into the expression system a control-supplying molecule which comprises a control sequence, which is not suppressed by the subject nucleic acid molecule and which encodes a detectable expression product, and wherein the control-supplying molecule is integrated into the target-expressing molecule.

Zeng, *et al.* teach the RNAi evaluation system comprising the pCMV-luc-Target-CAT plasmid, 293T cells, and miRNA-expressing and control plasmids as described above. Zeng, *et al.* do not teach quantifying target RNA by RT-PCR.

Wang, *et al.* teach that quantitative RT-PCR is more sensitive that northern blotting for RNA quantification as it allows for more accurate quantitative comparisons (first paragraph, p.198).

Kramer, *et al.* teach the general method of PCR, in which primers are designed to hybridize to a target region of interest. The authors teach that according to the purpose of the PCR, primers may be designed to contain mismatches or linkers that do not match the binding site at 100% complementarity (2nd to last paragraph on p. 15.1.7).

Ishaq, *et al.* teach intron-differential PCR wherein cDNA reverse-transcribed from mRNA is amplified via PCR (RT-PCR) with primers that span the introns allowing for discrimination of mRNA-derived amplification products from DNA-derived amplification products (see last paragraph of introduction, Results, p.8284, and Figure 1, p.8285).

It would have been obvious to one skilled in the art at the time of the instant application to design the claimed RNAi evaluation method to comprise a target-expressing molecule with primer-binding regions up- and down-stream of the target sequence for the purpose of detecting target cleavage by RT-PCR and to design at least one of the primer-binding regions to contain an intron. At the time of the instant application northern blot detection of RNA cleavage in RNAi evaluation systems was known, as evidenced by Zeng, *et al.* as described above, and RT-PCR was known to be a more sensitive means than northern blotting to quantify RNA, as taught by Wang, *et al.*, providing motivation to use RT-PCR for RNA detection in place of northern blotting. It was also known at the time of the instant application, according to Kramer *et al.*, that PCR primers could be designed according to the intended purpose of the PCR and could include additional sequences that were not complementary to the primer-binding region. It was also well-known at the time of the instant application that primers for RT-PCR could be designed to span an intron so that mRNA-derived amplification products, which lack introns due to splicing, could be distinguished from DNA-derived amplification products, which contain introns, as taught by Ishaq, *et al.* Thus, it would have been obvious to one of ordinary skill in the art at the time of the instant application to design an RT-PCR primer-binding region to contain an intron for the purpose of detecting only RNA-derived PCR products and not those that are DNA-

derived. Thus, the claims would have been obvious to one skilled in the art at the time of the instant application.

Closing

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Pitrak whose telephone number is 571-270-3061. The examiner can normally be reached on Monday-Friday, (9:00AM-5:00PM, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jennifer Pitrak
Patent Examiner
Art Unit 1635

Examiner, AU 1635

Notice to Comply	Application No.	Applicant(s)	
	10579906	NAITO ET AL.	
	Examiner	Art Unit	
	Jennifer Pitrak	1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☒ 7. Other: Seqeunces in the specification must be referred to with their respective sequence identifiers (SEQ ID NOs) as per 37 C.F.R. 1.821(d).

Applicant Must Provide:

☐ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☐ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the specification**.

☐ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

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